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Kenny-Caffey Syndrome in Six Bedouin Sibships: Autosomal Recessive Inheritance Is Confirmed

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We are reporting on 16 children, in 6 unrelated sibships, born to healthy, consanguineous parents of Bedouin ancestry. Eleven of them were assessed clinically. All presented with marked growth retardation, craniofacial anomalies, small hands and feet, hypocalcemia, hypoparathyroidism, radiological evidence of cortical thickening of long bones with medullary stenosis, and absent diploic space in the skull. There was a history of 6 affected sibs dying in infancy with hypocalcemic convulsions. All cases show absence of macrocephaly and early psychomotor retardation. The present cases confirm the presence of clinical variability and co firm autosomal recessive inheritance of Kenny-Caffey syndrome. Am. J. Med. Genet. 69:126–132, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: Kenny-Caffey syndrome; medullary stenosis and cortical thickening; psychomotor retardation; heterogeneity; autosomal recessive inheritance

INTRODUCTION

Since the original description of the Kenny-Caffey syndrome (KCS) [Kenny and Linerelli, 1966; Caffey, 1967] at least 28 patients have been reported [Francheschini et al., 1992]. More than half were familial with autosomal dominant inheritance [Kenny and Linerelli, 1966; Majewski et al., 1981], the remainder being sporadic and suggesting either new mutation or possible autosomal recessive inheritance [Frech and McAllister, 1968; Wilson et al., 1974; Bointon et al., 1979; Sarria et al., 1980; Weiland et al., 1981; Lee et al., 1983; Larsen et al., 1985; Fanconi et al., 1986]. Recently sibships with KCS suggesting an autosomal recessive mode of inheritance were reported [Francheschini et al., 1992]. The 11th edition of "Mendelian Inheritance in Man" [McKusick, 1994] included this syndrome among the autosomal dominant disorders (MIM 127000) with an unconfirmed autosomal recessive variant (MIM 244460). We report on 6 unrelated Bedouin sibships with KCS born to healthy consanguineous parents confirming the autosomal recessive form. The presence of early psychomotor retardation is a clue for clinical variability of the pleiotropic KCS gene.

CLINICAL REPORTS

Patient 1

E.A. (Fig. 1, family B: II-7) was born to healthy consanguineous parents of Bedouin origin, 8 years ago. She is the 7th child in a sibship of 11 children. Two of them (Fig. 1, family B: II-2 and II-6) died in infancy of hypocalcemic convulsions. There are two other similarly affected younger sibs (Fig. 1, family B: II-10 and II-11). Six remaining sibs are healthy.

She was born at term, after an uneventful antenatal period by breech presentation. Apgar score was 8 at one minute, and 9 at 5 minutes. Her weight was 2,000 g, OFC 30 cm and length 40 cm (< 10th centile). She was noted to have prominent forehead, small deep-set eyes, beaked nose, broad cheeks, and micrognathia. Upper limbs were relatively shorter than the body, with short fingers. Other systems were normal. At 2 days, she developed twitching movements of her face and limbs and was found to have hypocalcemia. Serum calcium level was 1.6 mmol/l, Mg 0.89 mmol/l and phosphate 3.5 mmol/l. Optimal serum calcium levels were reached only after administration of 1,2-alpha cholecalceferol drops at a dose starting with 0.5 mcg/Kg. Serum parathyroid hormone levels during the periods of hypocalcemia were less than 20 pg units/l which were inappropriately low. Results of thyroid, kidney and liver function tests were normal. Chromosome analysis did not show any abnormality. Hb was 15 g at birth. Radiological survey showed cortical thickening of long bones with medullary stenosis and absent diploic space in the calvaria (Figs. 2, 3, 4).

On follow-up, she continued to show extreme growth failure in spite of good nutrition. At 6 years her growth parameters remained far below the 3rd centile (Fig. 5) weight was 8 kg, OFC 43 cm, length 43 cm (Fig. 8A–C). There was no discrepancy between these

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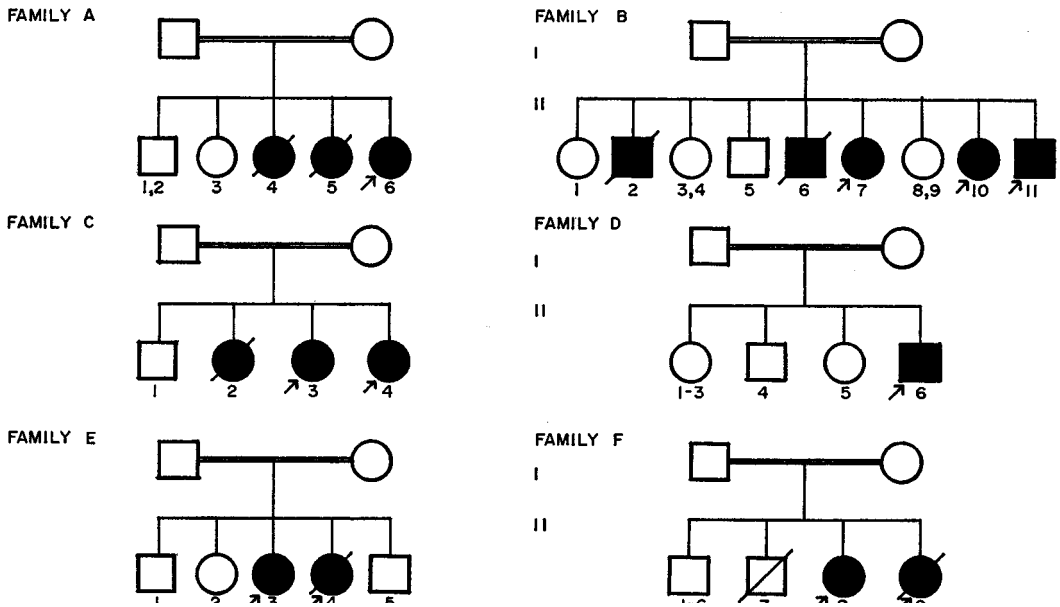

Fig. 1. Autosomal recessive Bedouin families with Kenny-Caffey syndrome.

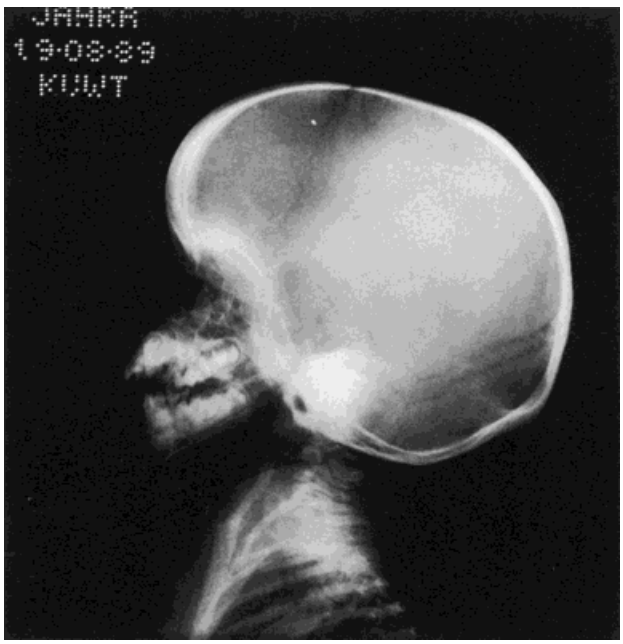

Fig. 2. Case 1. X-ray of skull showing absence of diploic space.

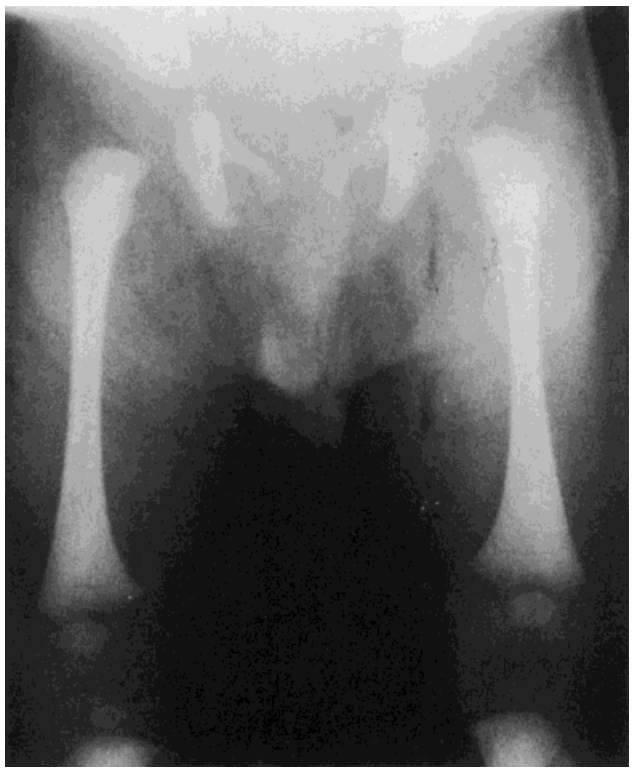

Fig. 3. Case 1. X-ray of long bones of the lower limbs showing cortical thickening of long bones.

parameters. Her hypocalcemia was controlled with calcium supplements and 1-alpha cholecalceferol drops which had to be increased in amount periodically. Apart from occasional twitchings there were no major convulsive episodes. Her psychomotor development was also noticeably retarded. At 6 years she had just started walking, was able to build a tower of 8 cubes, refer to self with a pronoun "I," and able to help in dressing. This puts her in the 33-month mental age group [Gesell, modified by Knoblock and Pasamanick, 1974].

CT scan of the head did not show any intracranial lesions. Her teeth erupted normally, but developed extensive caries (Fig. 6). Ophthalmic examination revealed small deep-set eyes, small corneae and hypermetropia. Hearing was found to be normal.

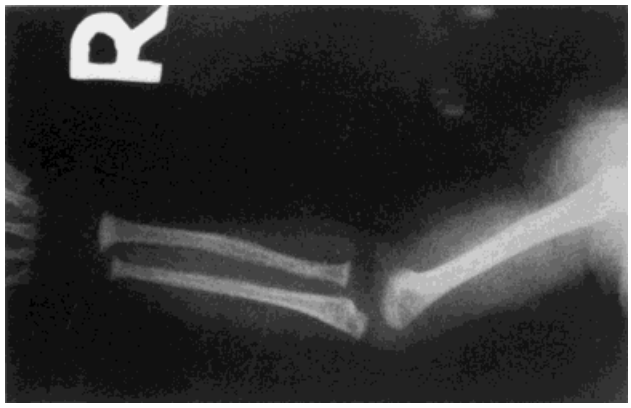

Fig. 4. Case 1. X-ray of long bones of upper limbs showing cortical thickening and medullary stenosis of long bones.

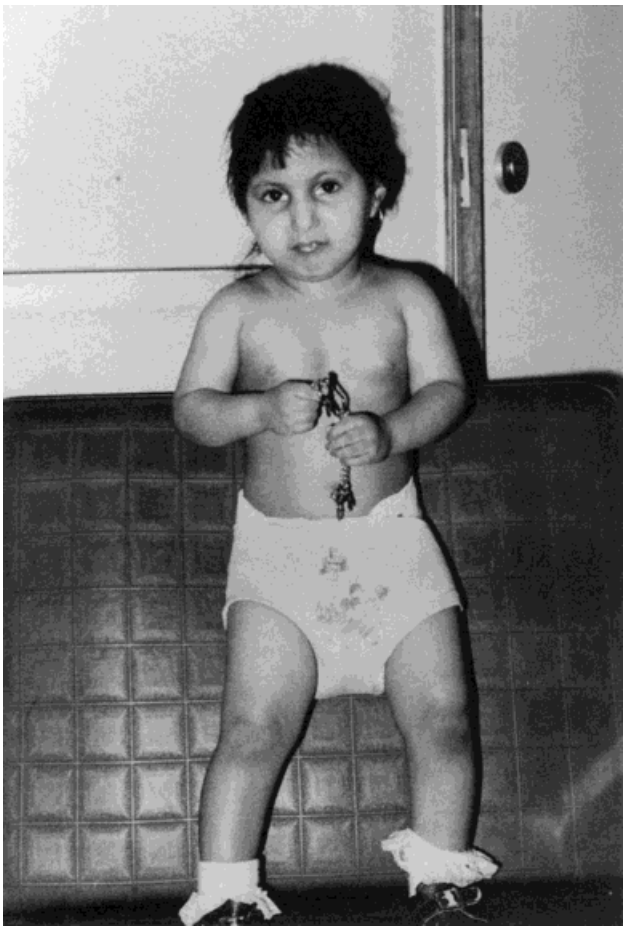

Fig. 5. Case 1, at 7 years, with extreme short stature.

Fig. 6. Case 1. Extensive dental caries.

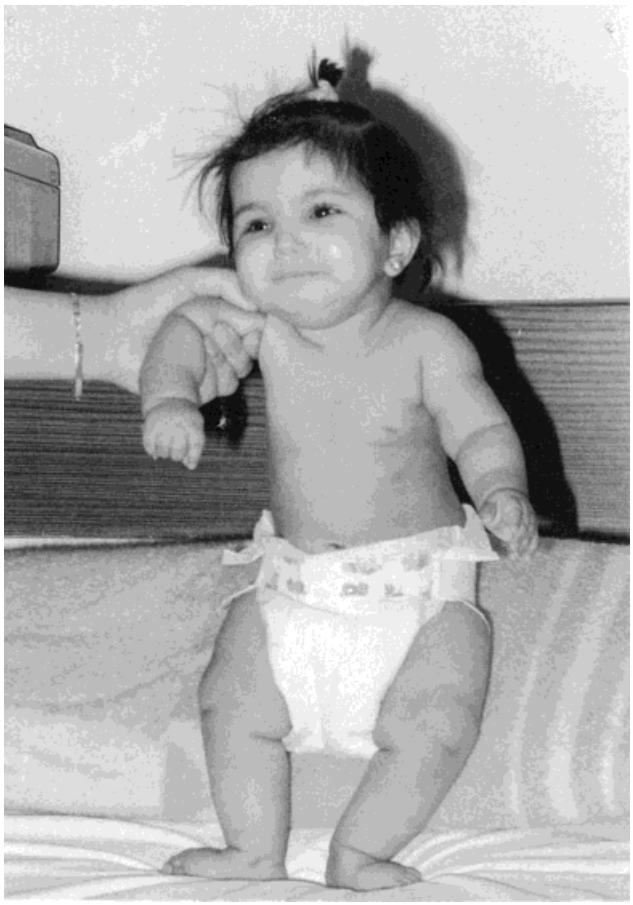

Fig. 7. Case 2 at 18 months of age.

Patient 2

I.A. (Fig. 1, family B: II-10) was born at term from a breech presentation. Intrauterine growth retardation was discovered at birth, as the mother did not attend antenatal follow-up. Apgar score was 7 at one minute and 9 at 5 minutes. Weight was 2,000 g, OFC 32 cm and length 42 cm (< 10th centile). She was noted to have the anomalies typical of KCS (Table I). Calcium levels were found to be low 1.5 mmol/l with normal Mg 0.8 mmol/l,

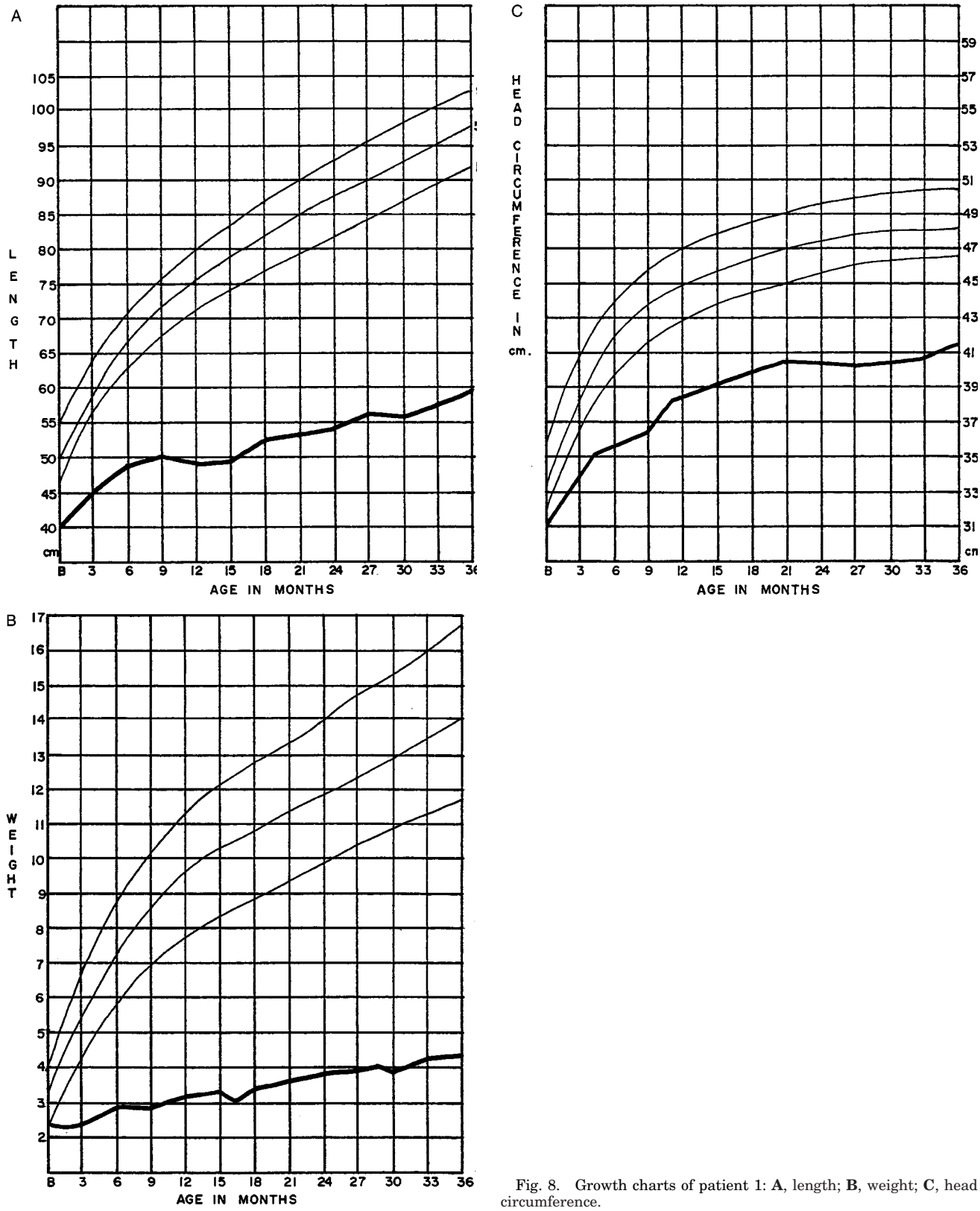

Fig. 8. Growth charts of patient 1: **A**, length; **B**, weight; **C**, head circumference.

TABLE I. Biological and Phenotypic Variables of 11 Bedouin Patients With Kenny-Caffey Syndrome

Families	A	B			C		D	E		F		Present study (11)		Reported cases (24)
Case (Fig. 1)	II-6	II-7	II-10	II-11	II-3	II-4	II-6	II-3	II-4	II-8	II-9	(%)		(%)
Age (yrs.)	8	6	2	3/12	2	3/12	10/12	5	7	7	4			
Sex (M:F)	F	F	F	M	F	F	M	F	F	F	F		2:9	6:7
Birth weight < 2.5 kg	+	+	+	+	−	+	+	+	+	+	+	10/11	90.9	30
Major manifestations														
Abnormal appearance	+	+	+	+	−	+	+	+	+	+	+	10/11	90.9	
Dwarfism	+	+	+	+	−	+	+	+	+	+	+	10/11	90.9	92.3
Delayed closure of fontanelle	−	−	−	−	−	−	−	−	−	−	−	−	nil	90.9
Psychomotor retardation	+	+	+		−		+	+	+	+	+	6/7	85.7	nil
Normal intelligence	−	−	−		+		−	−	−	−	−	1/9	11	88
Eye abnormalities	+	+	+	+	−	+	+	+	+	+	+	10/11	90.9	70.8
Dental caries	+	+	−	−	−	−	−	+	+	+	+	6/6	100	67
Biochemical														
Hypocalcemia	+	+	+	+	+	+	+	+	+	+	+	11/11	100	85.7
Hypocalcemia with tetany	+	+	−	+	+	+	+	+	+	+	+	10/11	90.9	59
Parathyroid hormone														
Low	+	+	+	+	+	+	−	+	+	−	+	9/11	81.8	58
High	−	−	−	−	−	−	+	−	−	−		1/11	9.09	46
Normal	−	−	−	−	−	−	−	−	−	+	−	1/11	9.09	
Radiological														
Cortical thickening and medullary stenosis of long bones	+	+	+	+	+	+	+	+	+	−	+	10/11	90.9	96.2
Absent diploic space in calvaria	−	+	+	+	−	+	+	+	+	−	+	8/11	72.7	86
Delayed bone age	+	+	−	−	−	+	+	+	+	−	+	7/11	63.6	60

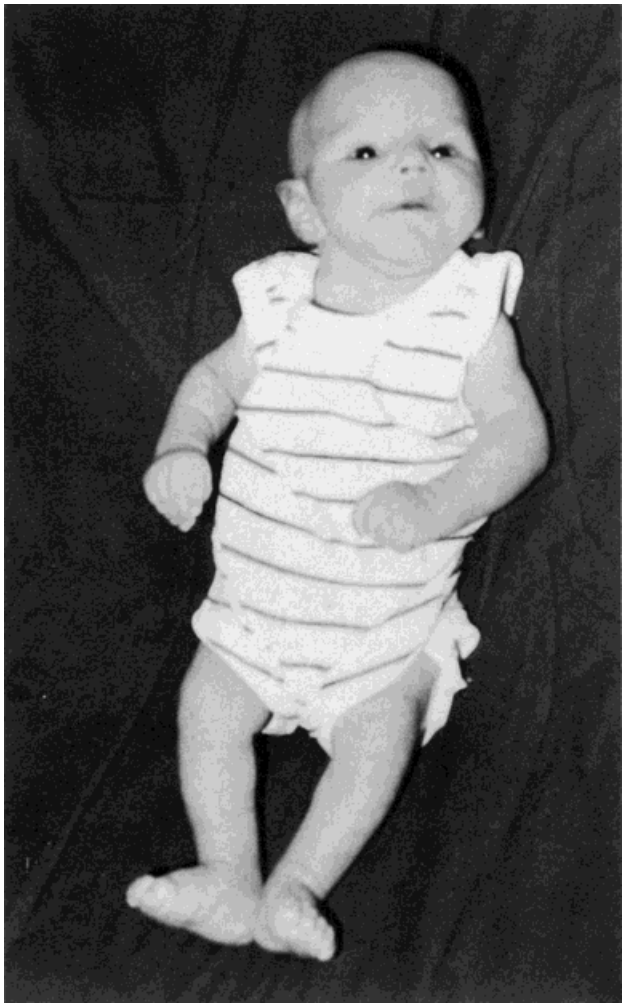

Fig. 9. Case 3 at 1 month of age.

and the phosphate level was 2.9 mmol/l. Parathormone level was 23 pg/ml which was inappropriately low. In spite of the low calcium levels, she was asymptomatic. Other systems were normal. Haematological survey showed her to be anemic for unknown reason. Bone marrow study was not successful because of cortical thickness of long bones. Radiologically, cortical thickening and medullary stenosis of long bones was noted. Results of thyroid, liver and renal functions were normal. Serum calcium levels were controlled with calcium supplements and 1-alpha cholecalceferol. Presently, at 18 months, there is evidence of growth and psychomotor retardation (Fig. 7).

Patient 3

S.A. (Fig. 1, family B: II-11) was born normally at term with severe intrauterine growth retardation. Apgar score was 8 at 1 min and 9 at 5 min. His weight was 1,800 g, OFC was 32 cm and length was 40 cm (< 10th centile). He had typical KCS (Fig. 9). Radiological survey showed cortical thickening and medullary stenosis of long bones. He presented with apnic attacks due to hypocalcemia. Serum calcium level was 1.8 mmol/l, serum parathyroid levels were found to be inappropriately low. At present he is 3 months old with a weight of 2,000 g, OFC of 32.5 cm and length of 40 cm. Results of thyroid and liver functions were normal. He has shown no evidence of psychomotor development.

Fig. 10. Third child from family E at age 5 years. Extreme short stature, microphthalmia, micromelic shortening.

Results of comprehensive clinical, biochemical and radiological assessment of the other cases in the 6 unrelated families are summarized in Table I. These show the presence of classical craniofacial findings. Hypocalcemia was consistent. Only 2 children were asymptomatic. Typical radiological findings of KCS were found in all children. Parathormone levels during the hypocalcaemic event were inappropriately low, except in one child. Delayed mental and motor development was present in all assessed cases. A 6-year-old child from family E (Table I) is another example of typical Kenny-Caffey syndrome (Fig. 10).

DISCUSSION

In the present study, 16 cases of KCS were diagnosed and registered at the Al-Jahra Regional Laision Community Genetic Programme serving a 250,000 inbred population mostly of Bedouin ancestry (more than 80% consanguineous). Clinical, radiological and biochemical aspects of the 11 assessed cases confirmed the diagnosis of KCS while the remaining 5 with similar pheno-

type died in early infancy with hypocalcemic seizures. Parental consanguinity in the 6 families with 16 KCS cases was 100% (Fig. 1).

In 1992, Francheschini et al. reviewed 28 patients with KCS including the original reports of Kenny and Linerelli [1966] and Caffey [1967]. The clinical, biochemical and radiological findings are compared with the data available in the present study (Table I). Normal intelligence and late closure of the anterior fontanelle with macrocephaly were prominent among the reported cases [Francheschini et al., 1992] in contrast to early closure of the anterior fontanelle, microcephaly and psychomotor retardation seen among our Bedouin patients. Interestingly, 8 other children with apparent KCS from 7 consanguineous families of Middle Eastern origin were reported with psychomotor retardation [Richardson et al., 1990]. In addition, most of them showed a predisposition to overwhelming sepsis. It seems that the KCS gene is a pleiotropic mutation with a wide spectrum of manifestations, involving various systems. At one end of the spectrum is the classical syndrome involving the skeletal and the endocrine system, manifested as short stature and hypocalcemia due to hypoparathyroidism but with normal intelligence. At the other end of the spectrum there are cases with additional involvement of the central nervous and immune systems [Richardson and Kirk, 1990]. Our patients fall between these two extremes with the typical findings of the KCS and developmental delay. This wide range of system involvement illustrates the clinical variability of the KCS pleiotropic gene. The inbred Bedouin family (Fig. 1, family B) with five KCS sibs of both sexes confirms autosomal recessive inheritance in this form of KCS.

REFERENCES

Bointon JR, Pheasant TR, Johnson BL, Levin DB, Straton BW (1979): Ocular finding in KCS. Arch Ophthalmol 97:896–900.

Caffey J (1967): Congenital stenosis of medullary spaces in tubular bones and calvaria in two proportional dwarfs—mother and son; coupled with transitory hypocalcemic tetany. Am J Roentgenol 100:1–11.

Fanconi S, Fischer JA, Wieland P, Atares M, Fanconi A, Giedion A, Prader A (1986): Kenny syndrome. Evidence for idiopathic hypoparathyroidism in two patients and for abnormal parathyroid hormone in one. J Pediatrics 109:469–475.

Francheschini P, Testa A, Bogeti G, Girardo E, Guala A, Lopez-Bell G, Buzio G, Ferrario E, Piccato E (1992): Kenny Caffey syndrome in two sibs born to consanguineous parents, evidence for an autosomal recessive variant. Am J Med Genet 42:112–116.

Frech RS, McAllister WH (1968): Medullary stenosis of tubular bones associated with hypocalcemic convulsions and short stature. Radiology 91:457–461.

Kenny FM, Linerelli L (1966): Dwarfism and cortical thickening of tubular bones. Am J Dis Child 111:201–207.

Knoblock H, Pasamanick B, eds. (1974): "Gesell and Amatrudas' Developmental Diagnosis," 3rd ed. Hagerstown, MD: Harper and Row.

Larsen JL, Kivlin J, Odell WD (1985): Unusual cause of short stature. Am J Med 78:1025–1032.

Lee BK, Vargas A, Barnes J, Root AW (1983): The Kenny-Caffey syndrome: Growth retardation and hypocalcemia in a young boy. Am J Med Genet 14:773–782.

Majewski F, Rosendahl W, Ranke M, Nolte K (1981): The Kenny syndrome. A rare type of growth deficiency with tubular stenosis, transient hypoparathyroidism and anomalies of refraction. Eur J Pediatr 136:21–30.

McKusick VA (1994): "Mendelian Inheritance in Man." 11th edition. Baltimore: Johns Hopkins University Press.

Richardson RJ, Kirk JMW (1990): Short stature, mental retardation and hypoparathyroidism: A new syndrome Arch Dis Child 65: 1113–1117.

Sarria A, Toledo F, Toledo J, Giteall AA (1980): Estenosis tubular diafisaria (sindrome de Kenny Caffey) presentacion de cautros observaciones. An Esp Pediatr 13:373–380.

Wieland P, Fischer JA, Haller R, Fanconi A, Prader A (1981): Severe dwarfism associated with hypocalcemia and unusual parathyroid hormone (PTH) findings (Abstr). Pediatr Res 15:1191A.

Wilson MG, Maronde RF, Mikity VG, Shinno NW (1974): Dwarfism and congenital medullary stenosis (Kenny syndrome). Birth Defects 10(12):129–132.